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Verification and Prediction of Solubilities of Active (Pharmaceutical) Ingredients In Solvents and Solvent Mixtures

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Solubilities of Active (Pharmaceutical) Ingredients (APIs or AIs – API is used below to represent both) are most likely one of the major concerns in the pharmaceutical, agrochemical, food and related industries because of the large use of solvents and anti-solvents in API-based production processes (solubilization, crystallization, etc.). A deep knowledge of the phenomena related to the systems API-solvent, API-solvent mixtures or API-additives-solvent(s) blends is necessary. Besides, the ever increasing search for new product (drug) formulations requires the availability of tools to verify and/or predict the API solubilities in different solvent systems.

Solids solubility in liquids is usually expressed, under certain assumptions, through the well-known Schroeder-van Laar equation (Prausnitz et al, 1999). Here, the functionality of the solid solubility from the system composition is taken into account through only the activity coefficient. In other words, in order to calculate the solubility of a solid in a solvent or liquid-mixture, with all the other parameters (enthalpy of fusion, melting temperature and temperature of the system) known, it is necessary to provide a correct and consistent value of the liquid phase activity coefficients. Therefore, a careful choice of the appropriate method to calculate these activity coefficients is extremely important. In addition, their temperature and composition dependence also needs to be correctly predicted.

Several liquid phase activity coefficient models have been used to achieve this task, such as NRTL, UNIQUAC, UNIFAC, NRTL-SAC, PC-SAFT and many more. These models are based on different principles and assumptions. In this work, three of them have been adopted, extended, and evaluated for API solubility. The UNIFAC (Fredenslund et al., 1977) is a group contribution-based model; the problem concerning this model is that often the group interaction parameters necessary to describe certain complex systems (such as API-solvents) are missing and the determination of these specific groups needs new experimental data. NRTL-SAC (Chen and Song, 2001; Chen and Crafts, 2006) and PC-SAFT (Gross and Sadowski, 2001), even though based on different principles, are both models with a correlative character since both need experimental data for the determination of the respective parameters, that is the conceptual segments for NRTL-SAC (hydrophilic, hydrophobic and polars) and binary interaction parameters for the PC-SAFT. A common point in the case of molecules such as APIs, is that experimental data are needed to regress the model parameters but the measurement of these data is often time-consuming, expensive and may even be infeasible in some cases. A full predictive model-based approach would make the solubility calculation procedure independent of experimental data, at least in the early stages of product-process evaluation. That is, a purely predictive approach is necessary.

In the proposed work a fully predictive model-based approach is developed based on the models UNIFAC, NRTL-SAC and PC-SAFT in order to compute the solubility (API solubility) in solvent and solvent mixtures. A group contribution method, GC+, based on the Marrero and Gani (2001) approach, has been developed to predict the pure component properties and parameters needed by the activity coefficient models for use in solubility calculations. A procedure based on atom connectivity indices is used to predict the missing UNIFAC group-interaction parameters. In addition, GC+ models are developed for predicting the conceptual segments of the NRTL-SAC model (thus avoiding the need for experimental data by this method) and the PC-SAFT molecular parameters. The presentation will highlight the solid solubility modelling developments together with various examples of API solubilities in single solvents and solvent mixtures. It will highlight the correct prediction of composition dependence (in case of solvent mixtures) and temperature dependence in case of single solvents and blends. Also, the effect of API solubility with respect to the addition of lipids will be highlighted because of the interest in such formulations.

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